TABLE I

LITHIUM ALUMINUM HYDRIDE REDUCTION PRODUCTS OF ω-CYCLOHEXYLALKYLKETENE DIMERS OF TYPE: $[C_6H_{11}(CH_2)_n—CHCO]_2$

n	Moles reagent per mole dimer	Formula	Yield, %	No. OH	B.p. °C.	Mm.	M.p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
0	1.8	$C_{16}H_{28}O_2$	21	0.82	145–148	4	58.5–60	76.2	76.6	11.1	11.4
1	1.7	$C_{18}H_{32}O_2$	62	.77	168–172	3	52.5–53.5	77.1	76.9	11.4	11.8
2	1.8	$C_{20}H_{36}O_2$[a]	45	.90	94–96	10		77.9	78.3	11.8	12.2
4	2.0	$C_{24}H_{44}O_2$	71	.89			39.5–40	79.1	78.8	12.1	12.0

[a] Refractive index ^{20}D 1.4771.

TABLE II

DERIVATIVES OF REDUCTION PRODUCTS OF TYPE (II)

n	3,5-Dinitrobenzoate Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Pyrazoline Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
0	$C_{23}H_{30}O_7N_2$	104–104.4	6.28	6.42	$C_{22}H_{30}N_4O_4$	64–65	13.5	13.7
1	$C_{25}H_{34}O_7N_2$	58–58.5	5.91	6.01	$C_{24}H_{34}N_4O_4$	109	12.7	12.3
2	$C_{27}H_{38}O_7N_2$	55–56	5.58	5.70	[a]			
4	$C_{31}H_{46}O_7N_2$[b]	59	5.02	5.20	$C_{30}H_{46}N_4O_4$	112–113	10.6	10.9

[a] Attempts to isolate the pyrazoline were unsuccessful. [b] *Anal.* Calcd.: C, 66.7; H, 8.24. Found: C, 67.2; H, 8.40.

Preparation of Substituted Pyrazolines.—Treatment of samples of the reduction products with 2,4-dinitrophenylhydrazine, in the usual manner, gave deep orange colored pyrazolines. Several modifications of this procedure failed to produce a suitable derivative of the reduction product where $n = 2$.

Analytical data of these derivatives are described in Table II.

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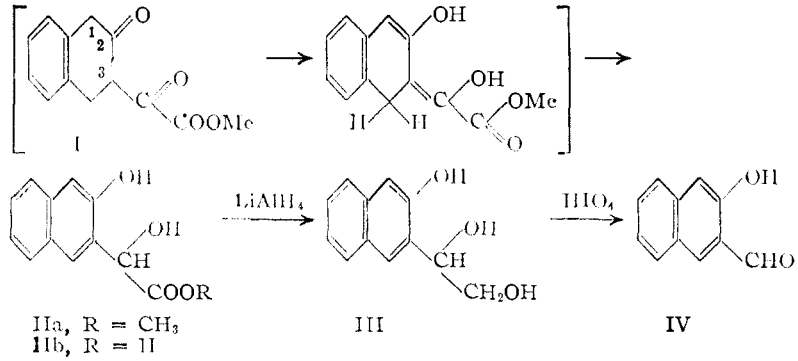
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF SMITH COLLEGE AND WELLESLEY COLLEGE, AND THE DYSON PERRINS LABORATORY OF OXFORD UNIVERSITY]

Some Unusual Reactions of 2-Tetralone

BY MILTON D. SOFFER, ROBERTA A. STEWART AND GRACE L. SMITH

Methoxide catalyzed condensation of dimethyl oxalate with 2-tetralone in non-polar media, results in substitution in the 3-position accompanied by dehydrogenation of the tetralone nucleus at the expense of the side chain. The structure of the product, methyl 3-hydroxy-2-naphthylglycolate, is shown by degradation. 2-Tetralone is smoothly converted to β-naphthol by the action of bromine.

Although the alkylation of 2-tetralone and its monocyclic analog, phenylacetone, proceeds exclusively[1,2] in the highly reactive position, C_1, ester condensation may take a different course. It has been shown recently that while formylation of phenyl acetone with ethyl formate occurs at C_3 in the presence of sodium alkoxide or sodamide in non-polar media (ether), the reaction in alcoholic sodium methoxide or ethoxide proceeds exclusively at C_1.[3] On the other hand, the only product reported from the condensation of phenylacetone with ethyl oxalate in the presence of ethanolic sodium ethoxide is the C_3-glyoxalate.[4]



In the present work it was shown that the glyoxalation of 2-tetralone, with methyl oxalate and dry sodium methoxide in benzene, occurs in the 3-position and takes a unique course. The crystalline product had the expected enolic properties, but failed to undergo elimination of carbon monoxide when heated with powdered soft glass.[5] The isolation of methanol from the latter treatment[5] precluded an initial lactone structure.

Inspection of the formula for the 3-glyoxalate (I) shows that it may be regarded as the fully ketonoid form of the phenolic hydroxy ester, IIa, which could arise from the glyoxalate by a series

(1) M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson and E. A. Bowler, THIS JOURNAL, **72**, 3704 (1950).

(2) C. M. Suter and A. W. Weston, *ibid.*, **64**, 533 (1942).

(3) M. Montagne, *Bol. inst. quim. Univ. Auton. Mex.*, **2**, No. 2, 57 (1946); *C. A.*, **44**, 130 (1950).

(4) H. Keskin, *Rev. faculté sci. univ. Istanbul*, Ser. A, **11**, No. 4, 143 (1946).

(5) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

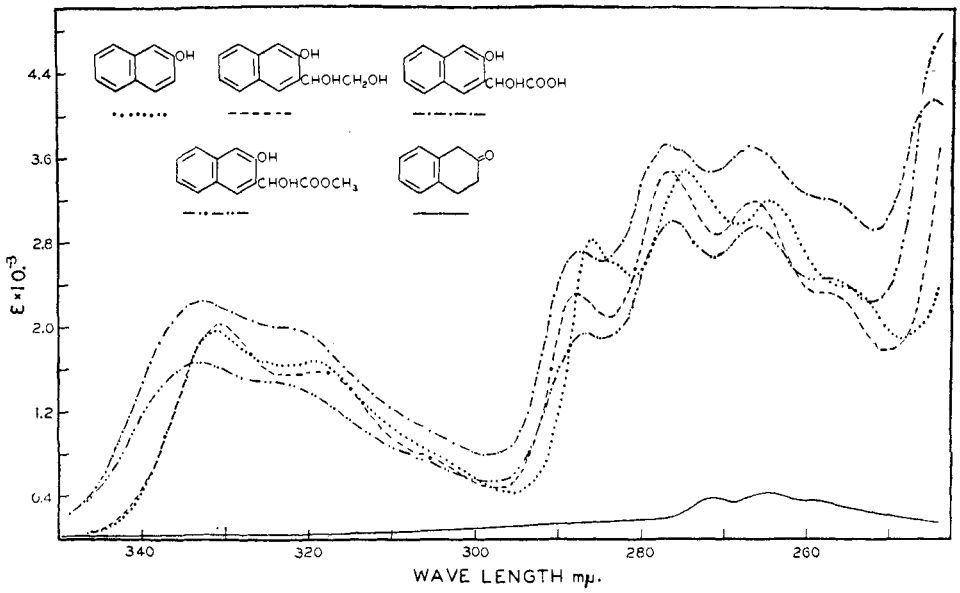


Fig. 1.—Absorption spectra in 95% ethanol.

of enolic tautomerizations. In line with this structure, IIa, the compound exhibited infrared absorption in the hydroxyl and ester carbonyl regions, but not in the ketone carbonyl region, and showed in the ultraviolet, absorption distinctly different from that of 2-tetralone but almost identical with that of β-naphthol (Fig. 1). The corresponding acid (IIb) and the reduction product (III, *vide infra*) showed similar absorption in the ultraviolet and also the characteristic bands for the functional groups in the infrared.

Each of these compounds formed a red precipitate with benzene diazonium chloride, indicating an unsubstituted 1-position. The structure shown, (IIa) was confirmed by reduction with lithium aluminum hydride to the crystalline triol, III, and conversion of the latter, by periodate cleavage, to 3-hydroxy-2-naphthaldehyde (IV), m.p. 99–100° [oxime, m.p. 207.5–208° (dec.)].[6]

The behavior of 2-tetralone on glyoxalation is in contrast with that of 1-tetralone, which gives the normal product.[7] In separate experiments[8] it was observed that 2-tetralone was smoothly converted to β-naphthol[9] under conditions[10] for the conversion of 1-tetralone to its 2-bromo derivative.

We wish to express our appreciation to the Research Corporation for a Frederick Gardner Cottrell Special Grant-in-Aid supporting this work.

Experimental[11]

Methyl 3-Hydroxy-2-naphthylglycolate (IIa).—The reaction was carried out according to the procedure of Bachmann, Cole and Wilds,[5] using dry sodium methylate from 4.09 g. (0.178 mole) of sodium, 100 ml. of anhydrous benzene, 20.06 g. (0.170 mole) of purified dimethyl oxalate and 23.71 g. (0.162 mole) of freshly prepared 2-tetralone. During the addition of the ketone the colorless solution turned red and finally brown and a large amount of crystalline material separated. After 2.5 hours at room temperature the mixture was refluxed for ten minutes. Excess ice-cold 6 *N* hydrochloric acid was added and the resulting solid filtered. The benzene solution, after washing with water and aqueous sodium bicarbonate, gave, on evaporation of the solvent, an additional amount of the glycolic ester. The crude product was recrystallized by dissolving in methanol and displacing most of the solvent with benzene at the boiling point, yielding 16.9 g. (45%) of material melting at 150–155°. An analytical sample melted at 153–154°; λ_{max}^{nujol}, 2.91 μ (hydroxyl), 5.77 μ (carboxylate).[12]

The white ester gave a green color with ferric chloride solution, reduced Tollens reagent, and formed a red precipitate with benzenediazonium chloride. With concentrated sulfuric acid it underwent a series of color changes: red, to orange, to gray-green, to blue-green, to blue, to purple.

Anal. Calcd. for $C_{11}H_9O_2(COOCH_3)$: OCH_3, 13.4; sapon. equiv., 232; mol. wt., 232. Found: OCH_3, 13.5; sapn. equiv., 231, 233; mol wt. (Rast), 235.

3-Hydroxy-2-naphthylglycolic Acid (IIb).—Two grams of the ester (IIa) was saponified by reaction with an excess of 2% sodium hydroxide at 0° for one hour. The acid was isolated in the usual manner (1.52 g., 81%), and recrystallized from methanol–benzene as described previously, and by further recrystallization from water; m.p. 166–166.5° (dec.), λ_{max}^{nujol}, 2.97 μ (hydroxyl), 5.77 μ (carboxylate).[12] This compound was also isolated from the sodium bicarbonate washings from the isolation of the glycolate ester (IIa). The pure white solid readily reduced Tollens reagent and formed a green color with ferric chloride solution. A solution of the acid in concentrated sulfuric acid turned from gray-green, to blue-green, to inky blue, to violet, and bubbles of gas were evolved.

Anal. Calcd. for $C_{11}H_9O_2(COOH)$: C, 66.05; H, 4.6; neut. equiv., 218. Found: C, 66.5, 66.6; H, 4.7, 4.8; neut. equiv., 221, 221.

3-Hydroxy-2-naphthylethylene Glycol (III).—In a flame-dried, three-necked flask, fitted with a dropping funnel, condenser and mercury-seal stirrer was placed 4.67 g. (0.123 mole) of lithium aluminum hydride and 150 ml. of dry

(6) The recorded melting points for the aldehyde and oxime are 99 and 207° (dec.) [T. Boehm and E. Profft, *Arch. Pharm.*, **269**, 25 (1931)]; for 2-hydroxy-1-naphthaldehyde the corresponding melting points are 84° [P. Ruggli and E. Burckhardt, *Helv. Chim. Acta*, **23**, 445 (1940)], and 148–150° or 158–160° [H. A. Torrey and C. M. Brewster, THIS JOURNAL, **35**, 426 (1913)].

(7) W. E. Bachmann and D. G. Thomas, *ibid.*, **63**, 598 (1941).

(8) We are indebted to Hilda E. Gellerson for these experiments.

(9) Dr. J. A. Barltrop of Oxford University has informed us that he has independently made the same observation.

(10) A. L. Wilds and J. A. Johnson, Jr., THIS JOURNAL, **68**, 86 (1946).

(11) All melting points are corrected.

(12) Randall, Fowler, Fuson and Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, 1949. We are indebted to Mr. Philip Sadtler of Samuel P. Sadtler and Son, Philadelphia, Pa., for the infrared determinations.

ether. Dry nitrogen was passed through the system, and the mixture was stirred for one-half hour. An ether solution of 9.45 g. (0.041 mole) of methyl 3-hydroxy-2-naphthylglycolate (IIa) was added dropwise to the milky-white suspension, at a rate sufficient to maintain reflux. The turbid reaction mixture was stirred overnight at room temperature. The excess lithium aluminum hydride was decomposed by the slow, dropwise addition of water. The yellow turbid solution was acidified with 150 ml. of 10% hydrochloric acid, and the enolic material isolated from the ether solution by the usual extraction procedure. The crude yellow crystalline triol, m.p. 148–149°, was obtained in quantitative yield (8.4 g.). After recrystallization, as mentioned previously from methanol–benzene, it melted at 152–153°; $\lambda_{max.}^{nujol}$, 2.81 μ (hydroxyl), no carbonyl absorption.[12]

The white product formed a bright green color with ferric chloride solution, reduced Tollens reagent, and yielded a red precipitate upon treatment with benzenediazonium chloride. The compound was unchanged by refluxing for two hours with semicarbazide hydrochloride in ethanol–pyridine.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 70.6; H, 5.9. Found: C, 70.3, 70.55; H, 6.0, 5.95.

One milliliter of acetic anhydride was added, dropwise, to a cold solution of 0.24 g. of the compound in 2 ml. of anhydrous pyridine, and the mixture was slowly brought to room temperature and then heated at 35° for one-half hour. Ice shavings were added and the product was extracted with ether and washed well with dilute hydrochloric acid, aqueous sodium carbonate, and finally with water. The white crystalline triacetate weighed 0.36 g. (93%). Recrystallization from benzene–petroleum ether (b.p. 30–60°) did not change the melting point, 87–87.5°, λ_{max}^{nujol}, 5.76μ (carboxylate), no hydroxyl absorption.[12]

Anal. Calcd. for $C_{12}H_9O_3(CH_3CO)_3$: C, 65.45; H, 5.5; CH_3CO, 39.1. Found: C, 65.8, 65.6; H, 5.4, 5.5; CH_3CO, 38.65, 38.9.

3-Hydroxy-2-naphthaldehyde (IV).—A solution of 268 mg. (0.116 mole) of potassium periodate in 15 ml. of 1 *N* sulfuric acid was added to a solution of 233 mg. (0.00114 mole) of the triol (III) in 12 ml. of 95% ethanol. After ten minutes the orange aldehyde was filtered, washed well with water, and dried; yield 0.12 g. (60%). Recrystallization from aqueous acetic acid gave pure yellow needles of the phenolic aldehyde, m.p. 99–100°.[6] The compound gave a green color with aqueous ferric chloride and formed a red-orange precipitate with benzenediazonium chloride.

The oxime was prepared quantitatively in pyridine–absolute ethanol, and was recrystallized from aqueous ethanol; m.p. 207.5–208° (dec.).[6] The pale yellow needles gave a blue color with ferric chloride solution.

Anal. Calcd. for $C_{11}H_9O_2N$: N, 7.5. Found: N, 7.3.

The Reaction between 2-Tetralone and Bromine.—An ether solution of 10.7 g. (0.073 mole) of 2-tetralone was treated with 11.66 g. (0.073 mole) of bromine according to the procedure[10] for the bromination of 1-tetralone. Evaporation of the washed extract gave 11.18 g. (106%) of crude 2-naphthol, m.p. 102–108°. Treatment with Norite and alumina, and recrystallization from ether–petroleum ether and benzene–petroleum ether gave the colorless halogen-free product, m.p. and m.m.p. 120–121°; picrate, m.p. 156.5–157.5° (recorded[13] m.p. 155.5°).

(13) O. L. Baril and E. S. Hauber, THIS JOURNAL, **53**, 1087 (1931).

NORTHAMPTON, MASSACHUSETTS
RECEIVED SEPTEMBER 26, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

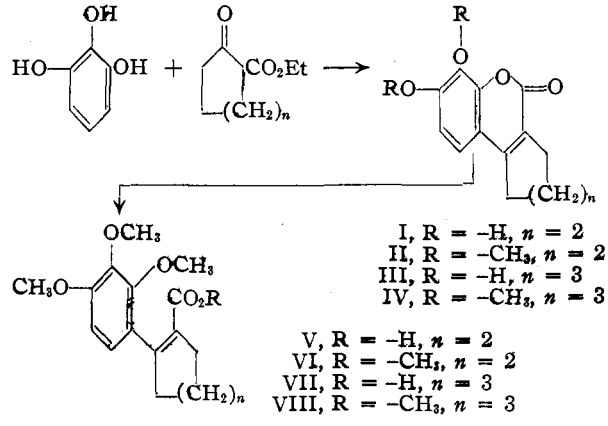
Coumarins as Intermediates in the Synthesis of Colchicine Analogs

BY V. BOEKELHEIDE AND FRANK C. PENNINGTON[1]

Exploratory work has been carried out to determine the usefulness of the von Pechmann coumarin condensation as a route to the synthesis of derivatives of colchicine. Although it has been possible to prepare a tricyclic molecule (XVI) having some of the structural features present in colchicine, difficulties encountered in attempts to prepare compounds more closely related to colchicine have not yet been resolved.

In a previous study of coumarins as synthetic intermediates[2] the suggestion was made that coumarins would be logical intermediates in the synthesis of molecules related to colchicine. The basis for this suggestion lay in the fact that the synthesis of hydrogenated colchicine derivatives requires the linking together of an alicyclic ring and a methoxylated aromatic ring, and the von Pechmann coumarin condensation is an excellent method for accomplishing this type of union. It is the purpose of this communication to report the results of some exploratory work based on this idea, including the synthesis of a tricyclic compound having some of the structural features present in colchicine.

Since any scheme involving the use of coumarins in a synthesis of this type would require at some stage in the scheme that the lactone ring of the coumarins be cleaved, our first experiments were directed toward the synthesis and ring-opening reactions of some model coumarins. As shown below, pyrogallol underwent condensation smoothly with 2-carbethoxycyclohexanone to give I in good yield. Methylation of I using potassium carbonate and methyl iodide readily gave II which, in turn, was converted to V by reaction with dimethyl sulfate and strong aqueous base. Although the ring-opening of coumarins using dimethyl sulfate and aqueous base can lead directly to the corresponding ester,[2] it proved to be a better procedure in this case to isolate the acid (V) and convert it to the ester (VI) by reaction with diazomethane.



I, R = –H, n = 2
II, R = –CH_3, n = 2
III, R = –H, n = 3
IV, R = –CH_3, n = 3

V, R = –H, n = 2
VI, R = –CH_3, n = 2
VII, R = –H, n = 3
VIII, R = –CH_3, n = 3

In view of the fact that ring C of colchicine is now

(1) Predoctoral Research Fellow, National Cancer Institute, Public Health Service, 1950–1951.

(2) V. Boekelheide and A. P. Michels, THIS JOURNAL, **74**, 256 (1952).